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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,489	SCHON, ERIC A.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-163* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-163* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant correctly notes that the restriction is moot in view of the preliminary amendment which is drawn only to method claims.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 90-163 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for for methods using closed, circular nucleic acid molecules, nucleic acid molecules with two fixed ends or linear molecules which exceed 800 nucleotides, does not reasonably provide enablement for linear molecules shorter than 800 nucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of mutation detection using circularizing oligonucleotides. The invention is is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of mutation detection. The method broadly encompasses the use of any nucleic acid and any mutation. More importantly, the claims encompass any length of nucleic acid, from an oligonucleotide that is 15 nucleotides in length to an entire chromosome. These molecules may have any structure ranging from linear to circular to catenated in more complicated ways.

Guidance in the Specification.

On page 17 of the specification there is a short discussion of the problem of slip through. "As described above, the target need not be a circle. Because the circularized oligo is small (less than 100 nt) and the
target is so big (16.6 kb for mtDNA), a large linear DNA (e.g. undigested or restriction-digested or sonicated nuclear DNA) is not likely to "slip through" the ligated oligo. Moreover, the intramolecular secondary structure of
the single-stranded target will also inhibit "slip-through." While the specification argues that slip through would not be likely to occur, no evidence or convincing reasons are

adduced to support that position. The specification lacks significant guidance on circularization of target or size limitations before slip through of linear molecules occurs

Quantity of Experimenation

The quantity of experimentation that would be necessary to determine what length, structure and sequence of linear target molecules and probes which could remain catenated to said target molecules for function of the assay is substantial.

Working Examples

There are no working examples of linear molecules being catenated and retained by the probe.

The unpredictability of the art and the state of the prior art

The fundamental problem is that slip through (where the molecules do not remain associated after ligation) is increasingly likely to occur on smaller, linear molecules. This is particularly true for targets smaller than the 16.6 kb of mitochondrial DNA, for which size or topological constraints may be less of an impediment to slip through of the target from the circular probe. There is some prior art (Nilsson et al (September 1994) Science 265:2085-2088) in which some evidence is shown that 150 nucleotide nucleic acid targets will not retain the probe (page 2087, column 1, paragraph 2). Nilsson also states that 850 nucleotide nucleic acid targets retained as much probe as uninterrupted strands, however Nilsson then states "The greater preservation of signal upon denaturing washes of probes bound to longer linear target molecules probably reflects the increased likelihood that target molecules were crosslinked to the membrane on both sides of the site where the probe was catenated (page 2087,m column 1,

paragraph 2)". This statement argues that probes would not have been retained without fixing of both ends to a membrane. There is no predictability for which lengths, sequences, or structures would be necessary to retain probe molecules. This unpredictability is due to the dependence of probe size and slip through of the probe, which was not examined in the specification nor in the prior art. For example, it is unclear whether a short or long probe would have greater slippage, since the short probe will have less topological problems to resolve, but be unable to pass by a large "knot" or structure in the DNA. A longer probe may have greater topological problems in moving along the target, but more easily pass the "knot" or structure of DNA. It is unpredictable whether these would rapidly move off DNA or do so slowly, and of course the minimum size of target DNAs necessary to retain the probes is completely unpredictable. There may also be dependence on the specific DNA sequence for movement, due to histone packing or other constraints.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching regarding slip through support a conclusion of undue experimentation. The specification provides one with no written description or guidance that leads one to a reliable method of avoiding slip through for smaller DNA targets, which are commonly used as targets. One of skill in the art cannot readily anticipate the effect of length changes of linear molecules for padlock probe type methods. Further the specification does not provide guidance to overcome art recognized problems in the use of padlock

probes as broadly claimed since Nilsson expressly shows that 150 nucleotide targets do not work. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of working examples with linear molecules and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Double Patenting

4. Claims 90-163 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-76 of U.S. Patent No. 5,866,337. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-76 of U.S. Patent No. 5,866,337 represent a species which have the proviso that linear molecules exceed 800 nucleotides and this species anticipates the current, more generic claims. Otherwise, the claims are virtually identical, with nearly identical dependent claims.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 90-92, 94, 95, 99-103, 106-108, 110, 115-119, 121-124, 127-128, 130, 135-140, 142-146, 148, 149, 151, 154-157, and 159-163 are rejected under 35 U.S.C. 102(a) as being anticipated by Nilsson et al (Science (September 1994) 265:2085-2088).

Nilsson teaches a method of detection of the cystic fibrosis transmembrane conductor f508 deletion mutation (page 2087, figure 3) which is correlated with a genetic disorder and also detection of neutral polymorphisms (page 2087, figure 4) comprising the steps:

a) contacting a target nucleic acid molecule with a circular probe which has two segments, a 5' end of a first segment and a 3' end of the second segment, that are linked by an oligonucleotide segment (page 2086, figure 1) and allowing hybridization of probe labelled either radioactively (page 2086, figure 2), enzymatically with horseradish peroxidase (page 2087, figure 3), or fluorescently with fluorescein (page 2087, figure 4) to the 7200 basepair circular DNA target nucleic acid (page 2086, figure 2)

b) contacting the hybridized product of (a) with a ligase and allowing ligation of the probe, which becomes catenated with the target nucleic acid molecule (see page 2086, figure 2),

c) detecting the catenated probe-target nucleic acid molecule complex indicating the presence of a mutation or neutral polymorphism (page 2085, column 1 and pages 2086-2087, figures 2-4).

With regard to claims 91, 92, 156, 157, Nilsson teaches the use of DNA and RNA (see page 2088, column 1).

With regard to claim 94, Nilsson teaches chromosomal DNA detection (see page 2087, figure 4).

With regard to claim 95, Nilsson eaches detection in M13, a viral DNA molecule (see page 2086, figure 2).

With regard to claim 99, 155, Nilsson shows ligation of the probe segments (see page 2086, figure 2).

With regard to claims 100-103, 121-124, 142-146, Nilsson shows the use of probe labelled either radioactively (page 2086, figure 2), enzymatically with horseradish peroxidase (page 2087, figure 3), or fluorescently with fluorescein (page 2087, figure 4).

With regard to claim 106-107, 116-119, 137-140, 148, 159-160, Nilsson shows a probe or nucleic acid which may be immobilized to a nylon affinity medium (page 2087, figure 3) or to a glass slide (page 2087, figure 4).

With regard to claim 108, 127-128, 149, 162, 163, Nilsson shows detection and capture of catenated nucleic acids(see page 2087, column 1).

With regard to claim 110, 130, 151, Nilsson shows detection of a deletion mutation (see page 2086, column 3).

With regard to claim 115, Nilsson shows detection of the CFTR deletion mutation, which is associated with a genetic disorder, using the method of claim 1 as discussed (see page 2086, column 3).

With regard to claim 135-136, 154, 161, Nilsson shows detection of neutral polymorphisms or of engineered polymorphisms using the padlock probe method of claim 1 (see figure 2, for example).

Nilsson also teaches "Moreover, immobilized padlock probes could be useful for preparative purposes, such as trapping circular target molecules from solution when screening gene libraries (page 2088, column 1, paragraph 2)".

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 93, 96, 104, 105, 120, 125, 126, 141, 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson in view of Matthews et al (Anal. Biochem. (1988) 169:1-25).

Nilsson teaches a method of detection of the cystic fibrosis transmembrane conductor f508 deletion mutation (page 2087, figure 3) which is correlated with a

genetic disorder and also detection of neutral polymorphisms (page 2087, figure 4) comprising the steps:

a) contacting a target nucleic acid molecule with a circular probe which has two segments, a 5' end of a first segment and a 3' end of the second segment, that are linked by an oligonucleotide segment (page 2086, figure 1) and allowing hybridization of probe labelled either radioactively (page 2086, figure 2), enzymatically with horseradish peroxidase (page 2087, figure 3), or fluorescently with fluorescein (page 2087, figure 4) to the 7200 basepair circular DNA target nucleic acid (page 2086, figure 2)

b) contacting the hybridized product of (a) with a ligase and allowing ligation of the probe, which becomes catenated with the target nucleic acid molecule (see page 2086, figure 2),

c) detecting the catenated probe-target nucleic acid molecule complex indicating the presence of a mutation or neutral polymorphism (page 2085, column 1 and pages 2086-2087, figures 2-4).

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With regard to claim 115, Nilsson shows detection of the CFTR deletion mutation, which is associated with a genetic disorder, using the method of claim 1 as discussed (see page 2086, column 3).

With regard to claim 135-136, 154, 161, Nilsson shows detection of neutral polymorphisms or of engineered polymorphisms using the padlock probe method of claim 1 (see figure 2, for example).

Nilsson also teaches "Moreover, immobilized padlock probes could be useful for preparative purposes, such as trapping circular target molecules from solution when screening gene libraries (page 2088, column 1, paragraph 2)".

Nilsson also does not explicitly demonstrate detection of chemiluminescent or magnetic probes nor the use of beads or probe bound to a solid support nor of other DNA types.

Matthews teaches the use of chemiluminescent (page 7, table 4) and magnetic (page 15, table 7) probes as well as the use of beads (page 15, table 7) and probe bound to a solid support (page 15, figure 8).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Nilsson with the refinements of Matthews since Matthews states "Various substances have been either used or advocated as labels for DNA probes (page 5, column 2, paragraph 3)". Matthews also states "The sandwich hybridization technique described below allows for the large scale preparation of an activated solid support coated with probe DNA (page 14, column 2, paragraph 4)". An ordinary practitioner would have been motivated to combine the teachings of Nilsson and Matthews for detection of nucleic assays with a broader ranger of potential probes, decreased material requirements and ease of automation using solid supports. An ordinary practitioner would also be aware that detection of mtDNA and cDNA are equivalent to detection of DNA when nucleic acid probes are used.

10. Claims 109, 111-114, 129, 131-134, 150, 152 and 153 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson in view of Thomas et al (U.S. Patent 4,749,647).

Nilsson teaches the limitations of claims 90-92, 94, 95, 99-103, 106-108, 110, 115-119, 121-124, 127-128, 130, 134-140, 142-146, 148, 149, 151, 154-157, and 159-163 as discussed above. Nilsson does not teach the equivalence of the different types of mutations in hybridization detection.

Thomas teaches that nucleic acid hybridization type assays are used to detect point mutations, deletions, translocations, insertions, inversions and other mutation types (see column 2, lines 55-64).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the detection method of Nilsson to detect different mutations types besides the deletion exemplified by Nilsson since these other mutations types are known equivalents in the prior art. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

11. Claims 97, 98 and 158 are rejected under 35 U.S.C. § 103 as being unpatentable over Nilsson in view of Stein et al (Cancer Res. (1988) 48:2659-2668).

Nilsson teaches the limitations of claims 90-92, 94, 95, 99-103, 106-108, 110, 115-119, 121-124, 127-128, 130, 134-140, 142-146, 148, 149, 151, 154-157, and 159-163 as discussed above. Nilsson does not teach the use of modified nucleotides.

Stein teaches the use of modified oligonucleotides in oligonucleotides (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Nilsson with the modified

oligonucleotides of Stein since Stein states regarding phosphorothioate oligonucleotides that "(a) they are relatively stable to cleavage by nucleases [factors up to several thousand have been reported]; (b) they have good aqueous solubility properties; (c) they show some depression of Tm and hence can be expected to hybridize well (page 2661, column 2 to page 2662, column 1)". An ordinary practitioner would have been motivated to combine the methods of Nilsson with the modified oligonucleotides of Stein for the benefits of greater stability, solubility, and superior hybridization.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman

JEFFREY FREDMAN
PRIMARY EXAMINER